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A Review on Novel Drug Delivery System

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Review Article

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ABSTRACT

The Niosomes are useful to increase drug efficacy. Niosomes are lamellar structures that are microscopic in size. The niosomes loaded drug is delivered on the specific site. The vesicle formulations have variable and controllable characteristics. The vesicle characteristic can be controlled by altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration.

INTRODUCTION

Treatment of diseases has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectable and suppositories as carriers from many decades. Drug absorption from the gastrointestinal tract is a complex procedure and makes in vivo performance of the drug delivery systems uncertain [1]. To maintain the concentration of drug administered within therapeutic range, there was a need to develop targeted drug delivery system to reduce the relative concentration of the drug in remaining tissues and the loss of drug due to localization of drug [2]. Targeted drug delivery was introduced by Paul Enrlich, in 1909, when he envisaged a drug delivery mechanism that would target directly to diseased cell [3]. Controlled release drug products are often formulated to provide the establishment and maintenance of any concentration at target site for longer intervals of time. [4]. These days, different carriers which are used for targeting of drug are immunoglobulins, serum, proteins, synthetic polymers, liposomes, microspheres, erythrocytes and niosomes. For an increasing range of modern drugs, toxicity towards key organs (e.g., liver, heart, kidneys) resulting from irregular delivery can lead to significant and sometimes unwanted side effects, thus limiting their therapeutic value [5]. Niosomes are one of the best among these carriers [5]. Niosomes and liposomes are similar in drug delivery potential and both increase drug efficacy as compared to that of free drug but niosomes are preferred over liposomes as the former exhibit high chemical stability and are economical [6].

NIOSOMES

Niosomes, non- ionic surfactant vesicles obtained on hydration, are microscopic lamellar structures prepared by combining non-ionic surfactant of alkyl or dialkylpolyglycerol ether with cholesterol [7]. Thermodynamically stable vesicles are formed only when proper mixture of surfactants and charge inducing agents is present [8].

Dr. Alec Bangham in 1965 had observed that handshake phospholipids dispersions in water form multilamellar spherical structures. These vesicles consist of an aqueous cavity encapsulated by one or more lipid bilayer membranes, soon which were named leptosomes [9]. In 1970s the self-assembly of non-ionic surfactants into vesicles was first reported by researchers in cosmetic industry [10]. The first niosome formulation was developed and patented by L'Oreal in 1975 [11].

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Structure of Niosomes

A typical niosome vesicle consists of a vesicle forming amphiphile i.e. a non-ionic surfactant such as Span-60. This vesicle is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle of niosomes[12]. They are vesicular systems that can be used as carriers for amphiphilic and lipophilic drugs. Hydration of film of a mixture of a single chain, non-ionic surfactant and cholesterol leads to formation of niosomes[13]. The addition of cholesterol leads to formation of ordered liquid phase which gives rigidity to the bilayers and hence less leakage of drug [14]. The figure 1 illustrates an idea about the structure of Niosomal vesicle [15].

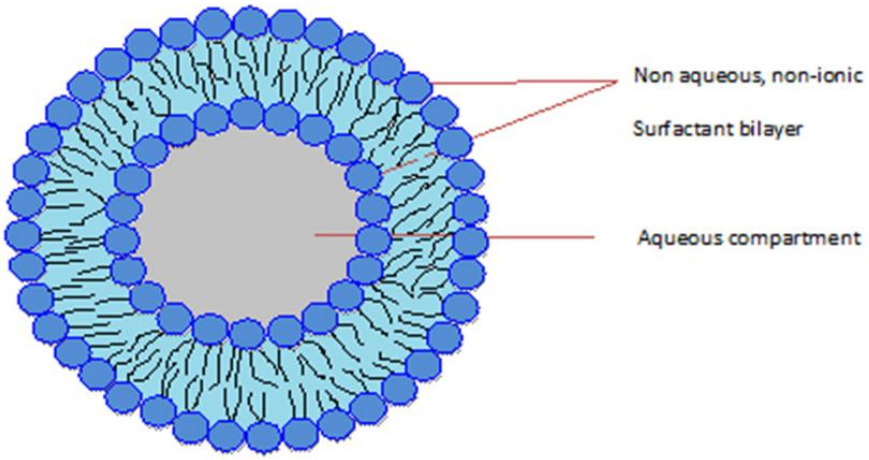

Figure 1: Structure of niosomes

Characteristic features of Niosomes

i. Niosomes are highly osmotically stable in nature and increase the stability of entrapped drug.

ii.Structurally, niosomes consist of hydrophobic and hydrophilic moieties together due to which drug molecules can be entrapped easily.

iii.The vesicle formulations have variable and controllable characteristics. The vesicle characteristic can be controlled by altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration.

iv.They improve bioavailability and therapeutic index of drug molecules.

v.Niosomes protect the drug from external natural environment.

vi.Niosomes are biodegradable, nontoxic, non-immunogenic and bon-carcinogenic.

vii.Niosomes do not require special conditions like low temperature or inert atmosphere for storage because they are quite stable structurally, even in the emulsified form.

viii.Niosomes can be made to target the site of action by oral, parenteral as well as topical routes.

ix.The vesicles may act as a depot for releasing the drug in a controlled manner.

x.Niosomes, being water based vesicle suspension, offer high patient compliance in comparison to oily dosage forms.

xi.They are more stable and economical than liposomes.

xii.Niosomes also serve as a better aid in diagnostic imaging and as a vaccine adjuvant.

xiii.The ability of non-ionic surfactant to form bilayer vesicles is dependent on the HLB value of the surfactant, the chemical structure of the components and the critical packing parameter and they are high resistance to hydrolytic degradation.

Niosomes Vs Liposomes

Liposomes are simple microscopic, concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids which are chemically unstable because they undergo oxidative degradation. It was discovered in 1960s by Bangham and coworkers they require special conditions for storage and handling and purity of natural phospholipids is variable. They are expensive. Niosomes are comparatively inexpensive; their ingredients non-ionic surfactants like, alkyl or dialkylpolyglycerol ether, are chemically stable because they do not undergo oxidative degradation. Niosomes are prepared from uncharged single chain surfactants. Therefore they do not require any special conditions of storage and handling and purity of non-ionic vesicles is not variable [16-22].

Types of niosomes

Niosomes are classified on the basis of number of layers they have (e.g. MLV, SUV), their size (e.g. LUV, SUV) and method of preparation (e.g. REV, DRV).

The various types of niosomes are mentioned below:

a) Multi lamellar vesicles
b) Large unilamellar vesicles
c) Small unilamellar vesicles.

Composition of Niosomes

The major components which are used for the preparation of niosomes are:

a. Cholesterol
b. Non-ionic surfactants
c. Others.

METHODS OF PREPARATION

Hand shaking method

The mixture of vesicles forming ingredients like surfactant and cholesterol are taken in the round bottom flask. These are dissolved in a volatile organic solvent such as diethyl ether, chloroform or methanol. The organic solvent is removed at room temperature (20°C) using rotary evaporator. A thin layer of solid mixture is deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This method is suitable for preparation of multilamellar vesicle niosomes. The approximate size of multilamellar vesicles is 0.5-10 µm (diameter) [23-25]. The aqueous phase containing drug is added slowly with occasional shaking of flask at room temperature followed by sonication [24,26].

Ether injection method

In this method niosomes are prepared by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60ºC. This mixture is injected into an aqueous solution of drug by 14-gauge needle. Single layered vesicles are formed by vaporization of ether. Depending upon the conditions used, the diameter of the vesicle can range from 50-1000 nm [27,28].

Sonication method

Sonication is a method of production of vesicles, in which 10 ml glass vial drug solution in buffer is added to the surfactant/cholesterol mixture in 10 ml glass vial. The mixture is probe sonicated at 60ºC for 3 minutes using a sonicator with titanium probe to yield niosomes. Small and unilamellar vesicles are formed by this method. By using sonication technique, size of niosomes formed by hand shaking can be reduced to 100-140 nm [29,30].

Reverse phase evaporation

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting emulsion are sonicated at 4-5°C. The emulsion is then dried to a semi-solid gel in a rotary evaporator under reduced pressure. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yieldniosomes. The vesicles formed are unilamellar and have diameter of 0.5µm [31-33].

Trans- membrane pH gradient (inside acidic) drug uptake process

Blend of surfactant and cholesterol are dissolved in chloroform in round- bottom flask (RBF) and chloroform is evaporated under reduced pressure to obtain a thin film on the wall of the flask. The film is hydrated by vortex mixing with 300 mM citric acid (pH 4.0). The multilamellarvesicles are frozen and thawed three times and then sonicated. Aqueous solution containing 10 mg/ml of drug is added to this niosomal suspension and vortexed. The pH of the sample is raised to 7.0- 7.2 with 1M disodium phosphate and the mixture is then heated at 60ºC for 10 minutes to produce the desired multilamellar vesicles [34-36].

The "Bubble" method

This technique has recently been developed which allows the preparation of niosomes without use of organic solvents. It consists of an RBF with three necks, positioned in a water bath to control the temperature. Thermometer is placed in the first and second neck of the flask, while the third neck is used to supply nitrogen. Cholesterol and surfactant are dispersed together in a buffer (pH 7.4) at 70°C. This dispersion is mixed for a period of 15 seconds with high shear homogenizer and immediately afterwards, it is bubbled at 70°C using nitrogen gas to yield niosomes [37].

Formation of niosomes from proniosomes

In this method niosomes are prepared by coating a water soluble carrier such as sorbitol with surfactant. This results in formation of dry formulation. The water soluble particles covered with the dry surfactant are termed as "Proniosomes". This leads to rapid reconstitution of niosomes with minimum residual carrier. The niosomes recognize by the addition of aqueous phase at temperature greater than phase transition temperature (T > Tm) and brief agitation [38].

T = temperature

Tm= mean phase transition temperature

Figure 2: Structure of niosomes

Micro fluidization

Micro fluidization is a recent technique in which defined sized unilamellar vesicles are prepared. In this method two fluidized streams interact at ultra-high velocities based on submerged jet principle, within defined micro channels in the interaction chamber. The impingement of thin liquid sheet along a common front is arranged in such manner so that the energy supplied to the system remains within the area of niosomes formation. Niosomes formed have greater uniformity, smaller size and better reproducibility.

Multiple membrane extrusion method

In this method, the mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is formed into thin film by evaporation. This film is hydrated with aqueous solution of drug and the resultant suspension extruded through polycarbonate membranes. These membranes are placed in series for upto 8 passages. It leads to formation of niosomes with controlled size.

CHARACTERIZATION OF NIOSOMES

Vesicle size

Niosomal size ranges from around 20 nm to 50 µm. Niosomes with diameter over 1 µm, can be adequately measured by light microscopy and coulter counter method. Light microscopy offers the possibility of collecting information on particle shape, whereas the volume distribution of niosomes (>1 µm) in dispersions can be determined with Coulter counter.

Niosomal drug loading and encapsulation efficiency

The niosomal aqueous suspension is ultra-centrifuged, supernatant is removed and sediment is washed twice with distilled water in order to remove absorbed drug which helps to determine drug loading and encapsulation efficiency. The niosomal recovery is calculated as:

$$Niosomal\ recovery\ (\%) = \frac{Amount\ of\ niosomes\ recovered}{Amount\ of\ polymer} + drug + excipient$$

Unentrapped drug is separated by dialysis, centrifugation or gel filtration, after preparing niosomal dispersion. The amount of entrapped drug in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug. The formulae for entrapment efficiency given below,

$$\text{Entrapment efficiency (EF)} = \frac{\text{Amount entrapped}}{\text{total amount}} \text{x} 100$$

HLB (hydrophilic-lipophilic balance) value

HLB value affects entrapment efficiency, such that HLB value of 14 to 17 is not suitable for niosomes but HLB value of 8.6 has highest entrapment and it decreases with decrease in HLB value from 8.6 to 1.73.

Bilayer rigidity and homogeneity

The bio-distribution and biodegradation of niosomes are influenced by rigidity of the bilayer. The homogeneity could be identified via NMR (Nulcear Magnetic Resonance), differential scanning calorimetry (DSC) and fourier transform-infra red spectroscopy (FT-IR) techniques. Recently, florescence resonance energy transfer (FRET) has been used to determine the shape, size and structure of the niosomes.

In-vitro release

In- vitro release rate study includes the use of dialysis tubing in which dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted out into a bag and sealed. The bag containing vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. The buffer is analyzed for the drug content by an appropriate assay method.

FACTORS AFFECTING THE PHYSICOCHEMICAL PROPERTIES OF NIOSOMES

Nature of surfactants

The surfactant used for the preparation of niosomes must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group. The ether type surfactants with single chain alkyl hydrophobic tail is more toxic than corresponding dialkyl ether chain. The ester type surfactants are chemically less stable than ether type surfactants. The ester type surfactants are less toxic than the ether type surfactants due to ester-linked surfactant degraded by esterases to trigycerides and fatty acid in vivo. With an increase in the HLB of surfactants such as span 85 (HLB 1.8) to span 20 (HLB 8.6), there is an increase in the mean size of niosomes.

Structure of surfactants

Structure of surfactants affect the geometry of vesicle formed, which is related to critical packing parameters. Critical packing parameters can be defined using following equation,

$$\text{CPP (Critical Packing Parameters)} = \frac{\text{v}}{\text{lc}} * \text{ao}$$

Where, v = hydrophobic group volume,
lc = the critical hydrophobic group length,
a0 = the area of hydrophilic head group.
From the CPP value, type of micelle structure formed can be ascertained as given below,
If CPP <0.5, then spherical micelles are formed.
If 0.5 < CPP <1, then inverted micelles are formed.

Membrane composition

With the addition of different additives along with surfactants and drugs, stable niosomes can be prepared. The morphology, permeability and stability properties are altered by manipulating different additives e.g. rigidity of niosomal system can be increased by addition of cholesterol and drug permeability through membrane is decreased. In case of polyhedral niosomes prepared by C16G2/ cholesterol/ MPEG- Chol, the shape of noisome remains unaffected by adding low amount of Solulan C24(cholesteryl poly-24- oxyethylene ether), which prevents

aggregation due to development of steric hindrance and results in spherical vesicles with diameter ranging from 20 nm to 200 nm.

Cholesterol content and charge

The incorporation of cholesterol into bilayer composition of niosomes increases the membrane stabilizing activity and decrease the leakiness through. At a high cholesterol concentration, the gel state is transformed to a liquid –ordered phase. An increase in cholesterol content of bilayers results in decreased release of encapsulated material, due to an increase in rigidity of the resulting bilayer. In multilamellar vesicles, the interlamellar distance between successive bilayers, increases due to presence of charge and leads to greater overall entrapped volume.

Resistance to osmotic stress

Diameter of vesicles in suspension of niosomes is reduced on addition of hypertonic solution. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles followed by faster release, due to inhibition of eluting fluid from vesicle, which may be due to mechanical loosening of vesicles structure under osmotic stress.

Temperature of hydration

Hydration temperature influences the shape and size of the noisome. It should be above the gel to liquid phase transition temperature of system for ideal condition. Change in temperature of niosomal system affects assembly of surfactants into vesicles and induces vesicles shape transformation [38-45].

Nature of encapsulated drug

The encapsulated drug influences charge and rigidity of the niosomal bilayer. On interaction with surfactant head groups, charge develops that creates mutual repulsions between surfactant bilayers and hence increases the vesicle size. The aggregation of charged vesicles is prevented due to charge development on the bilayer. Some drug is entrapped in the long polyoxyethylene glycol (PEG) chains in PEG vesicles, thus reducing the tendency to increase the size. The degree of drug entrapped is affected by HLB of the drug.

Table 1: Effect of drug on the formation of niosomes.

Nature of the drug	Leakage from the vesicles	Stability	Other properties
Hydrophobic drug	Decreased	Increased	Improved transdermal delivery
Hydrophilic drug	Increased	Decreased	
Amphiphilic drug	Decreased	-	Increased encapsulation, altered electrophoretic mobility
Macromolecules	Decreased	Increased	

Method of preparation

Vesicles with small diameter are formed by ether injection method (50-1000 nm) as compared to hand shaking method (0.35-13 nm). Small-sized niosomes can be prepared by reverse phase evaporation while by micro fluidization, greater uniformity and small sized vesicles are obtained.

SEPARATION OF UNENTRAPPED DRUG

The unentrapped solute from the vesicles can be removed by various techniques, which include:

Dialysis: The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.

Gel Filtration: The unentrappeddrug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

Centrifugation: The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then re-suspended to obtain a niosomal suspension free from unentrapped drug.

Table 2: Advantages and disadvantages of different methods of separation of entrapped drug from the un-entrapped drug.

Separation Method	Advantages	Disadvantages
Dialysis	Suitable for large vesicles >10μm, suitable for highly viscous system, Inexpensive	Extremely slow (5-24 hrs), dilutes the niosome dispersion, Large volumes of dialysate required.
Centrifugation (below 7000 x g)	Quick (~ 30 min), inexpensive instrumentation concentrates niosome dispersion	Fails to sediment the sub micronniosomes, may lead to the destruction of fragile systems.
Ultracentrifugation (15,000×g)	Sediments all size populations, concentrates the niosomedispersion	Expensive instrumentation, long centrifugation times (1-1.5 h), may lead to destruction of fragile systems, may lead to formation of aggregates.
Gel Filtration	Quick (4-5 min) with sephadex G50)	Slow (1-2 h) when using Sepharose for macromolecule separation. Gels are expensive when not used. Not suitable for highly viscous formulations.

APPLICATIONS

NSAIDs

The niosomal formulations of various NSAIDs for example aceclofenac, diclofenac sodium, ketoprofen, flurbiprofen, indomethacin and meloxicam have better properties, like entrapment efficiency, therapeutic efficacy, permeation, bioavailability and less toxicity as compared to the other formulations [46-50].

Neoplasia

Numerous attempts have been made to enhance the selectivity of antineoplastic agents by linking them to cancer moiety. Cisplatinniosomes are protective against weight loss and have reduced bone marrow toxicity as compared to free cisplatin [51-56].

Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without triggering the side effects, and thus allowed greater efficacy in treatment [57-60].

Targeting bioactive agents

Reticulo-endothelial system (RES): The non-ionic vesicles are preferentially taken up the cells of RES. This localized drug accumulation has however, been used in treatment of animal tumours known to metastasize to the liver and in parasitic infestation of liver [61-65].

Organs other than RES: The non-ionic vesicles can also be directed to specific sites in the body by the use of antibodies. Immunoglobulins can bind readily to the lipid surface of carrier system, thus offering a convenient path for targeting of drug carrier. Large numbers of cells possess intrinsic ability to bind particular carbohydrate determinants and thus they can be exploited by direct carrier systems to specific cells [66-68].

Delivery of Peptide Drugs

Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in-vitro study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide [68-71].

Cosmetic delivery

Niosomes in cosmetic and skin care applications show their ability to increase the stability of entrapped drugs, improved bioavailabilty of poorly absorbed ingredients and enhanced skin penetrations. The results suggest that niosomalformulations could constitute a promising approach for the topical delivery of minoxidil in hair loss treatment [71-75].

Use in studying immune response

Niosomes are being used to study the nature of the immune response provoked by antigens. Nonionic surfactant vesicles have clearly demonstrated their ability to function as adjuvant following parenteral administration with a number of different antigens and peptides. Many niosomal formulations have been used for determining the nature of the immune response produced by antigens. It has been studied that niosomal vesicles are potent adjuvant in terms of immunological selectivity, and also have low toxicity and greater stability [75-79].

Niosome formulation as a brain targeted delivery system for the vasoactive intenstinal peptide (VIP)

Animal studies conducted with radiolabelled (I-125) VIP- loaded glucose bearing niosomes showed that when given intravenously, encapsulated VIP within these niosomes have higher vasoactive intestinal peptide (VIP) brain uptake as compared to control [80-85].

Niosomes as carriers for Hemoglobin

Niosomes can be used as carriers for haemoglobin within the blood. These vesicles are permeable to oxygen and hemoglobin, hence can act as a carrier for haemoglobin in anaemic patients [86-90].

Antifungal agents

Niosomal formulations have increased bioavailability and activity of various antifungal drugs, such as griseofulvin, which has poor and variable oral bioavailability and is improved by using different methods of preparation, varying surfactants and cholesterol concentration of niosomes. An alternative formulation was developed for the vignal administration of clotrimazole to provide sustained and controlled release for local vaginal therapy by formulation in niosomes [90-93].

Pulmonary delivery

Inhalation therapy is used for asthmatic patients but is limited because of poor permeation of drug through the hydrophilic mucus. To overcome this, niosomes of poly-sorbate 20 were prepared, which contain beclomethasonedipropionate. They examined that the Niosomes showed sustained and targeted delivery and also improved mucus permeation. Therefore therapeutic effect is improved [94-97].

Diagnostic imaging with niosomes

Vesicles are also considered as a carrier for diagnostic agent iobitridol for X-ray imaging. These vesicles are prepared by using the thin film hydration method followed by sonication. This method allows increased encapsulation and stability of niosomes [98-100].

CONCLUSION

Niosomes provide constant and prolonged therapeutic effect. Niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. Proniosomes is a novel concept in which drug delivery potential of niosomes can be enhanced. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Various types of drug deliveries such as targeting, ophthalmic, topical, parenteral, can be possible using niosomes. Niosomes improve bioavailability of poorly absorbed ingredients which enhance skin penetrations.

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